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MDA-MB-175 cells or from another source, such as another animal species, but also the polypeptide prepared by recombinant or synthetic methods. It also includes variant forms including functional derivatives, allelic variants, naturally occurring isoforms and analogues thereof. Sometimes the γ -HRG is "native γ -HRG" which refers to endogenous γ -HRG polypeptide which has been isolated from a mammal. The γ -HRG can also be "native sequence γ -HRG" insofar as it has the same amino acid sequence as a native γ -HRG (e.g. human γ -HRG shown in FIG. 7A-7C). Amino acid sequence variants of the native sequence are prepared by introducing appropriate nucleotide changes into the native sequence DNA, or by in vitro synthesis of the desired polypeptide. Such variants include, for example, deletions from, or insertions or substitutions of, residues within the amino acid sequence shown for the human protein in FIG. 7A-7C as generally described above for other heregulin. Any combination of deletion, insertion, and substitution is made to arrive at the final construct, provided that the final construct possesses the desired characteristics. The amino acid changes also may alter post-translational processes of the native sequence, such as changing the number or position of O-linked glycosylation sites.

IN THE CLAIMS

Please cancel claim 13.

Please amend claims 1-7, 9, and 14-17 to read as follows:

1. (Amended) A method of inducing hair cell generation or inner-ear-supporting cell growth, regeneration, and/or proliferation, comprising contacting an inner-ear-supporting cell which expresses HER2 and/or HER3 receptors with an effective amount of an isolated ligand which activates HER2 and/or HER3 receptors, said isolated ligand comprising a heregulin polypeptide selected from the group consisting of heregulin- β 2 (SEQ ID NO: 5), heregulin- β 2-like polypeptide (SEQ ID NO: 9), heregulin- β 3 (SEQ ID NO: 7), heregulin γ (SEQ ID NO: 11), heregulin- α (SEQ ID NO: 1) variants, heregulin- β 1 (SEQ ID NO: 3) variants, heregulin- β 2 (SEQ ID NO: 5) variants, heregulin- β 2-like polypeptide (SEQ ID NO: 9) variants, heregulin- β 3 (SEQ ID NO: 7) variants, heregulin γ (SEQ ID NO: 11) variants, heregulin- α (SEQ ID NO: 1) fragments, heregulin- β 1 (SEQ ID NO: 3) fragments, heregulin- β 2 (SEQ ID NO: 5) fragments, heregulin- β 2-like polypeptide (SEQ ID NO: 9) fragments, heregulin- β 3 (SEQ ID NO: 7)

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fragments, heregulin γ (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments.

2. (Amended) The method of claim 1, wherein the activating ligand is a heregulin- α variant, heregulin agonist antibody or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- α variant is selected from the group of heregulin- α variants having an amino acid substitution, deletion or insertion at one or more amino acid residues corresponding to positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, 43, 45, 46, 48, 49, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226-254, 256-265, 272, 273, 278, 279, 285-309, 437, and 608- 611 in the heregulin- α amino acid sequence of SEQ ID NO: 1.

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cont.

3. (Amended) The method of claim 1, wherein the activating ligand is a human heregulin polypeptide or a fragment thereof.

4. (Amended) The method of claim 1, wherein the activating ligand is selected from the group consisting of HRG- α variants, $-\beta 1$ variants, $-\beta 2$, $-\beta 2$ variants, $-\beta 2$ -like polypeptide, $-\beta 2$ -like polypeptide variants, $-\beta 3$, and $-\beta 3$ variants, and fragments thereof.

5. (Amended) The method of claim 1, wherein the activating ligand is γ -HRG or a variant or a fragment thereof.

6. (Amended) The method of claim 1, wherein the activating ligand is a recombinant human heregulin polypeptide or a fragment thereof.

b3 b6 b7 b8 b9 b10 b11 b12 b13 b14 b15 b16 b17 b18 b19 b20 b21 b22 b23 b24 b25 b26 b27 b28 b29 b30 b31 b32 b33 b34 b35 b36 b37 b38 b39 b40 b41 b42 b43 b44 b45 b46 b47 b48 b49 b50 b51 b52 b53 b54 b55 b56 b57 b58 b59 b60 b61 b62 b63 b64 b65 b66 b67 b68 b69 b70 b71 b72 b73 b74 b75 b76 b77 b78 b79 b80 b81 b82 b83 b84 b85 b86 b87 b88 b89 b90 b91 b92 b93 b94 b95 b96 b97 b98 b99 b100 b101 b102 b103 b104 b105 b106 b107 b108 b109 b110 b111 b112 b113 b114 b115 b116 b117 b118 b119 b120 b121 b122 b123 b124 b125 b126 b127 b128 b129 b130 b131 b132 b133 b134 b135 b136 b137 b138 b139 b140 b141 b142 b143 b144 b145 b146 b147 b148 b149 b150 b151 b152 b153 b154 b155 b156 b157 b158 b159 b160 b161 b162 b163 b164 b165 b166 b167 b168 b169 b170 b171 b172 b173 b174 b175 b176 b177 b178 b179 b180 b181 b182 b183 b184 b185 b186 b187 b188 b189 b190 b191 b192 b193 b194 b195 b196 b197 b198 b199 b199 b200 b201 b202 b203 b204 b205 b206 b207 b208 b209 b2010 b2011 b2012 b2013 b2014 b2015 b2016 b2017 b2018 b2019 b2020 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14. (Amended) A method of increasing the number of inner-ear-supporting cells, comprising administering to a patient in need thereof an effective amount of an isolated HER2 and/or HER3 activating ligand comprising a heregulin polypeptide selected from the group consisting of heregulin- β 2 (SEQ ID NO: 5), heregulin- β 2-like polypeptide (SEQ ID NO: 9), heregulin- β 3 (SEQ ID NO: 7), heregulin γ (SEQ ID NO: 11), heregulin- α (SEQ ID NO: 1) variants, heregulin- β 1 (SEQ ID NO: 3) variants, heregulin- β 2 (SEQ ID NO: 5) variants, heregulin- β 2-like polypeptide (SEQ ID NO: 9) variants, heregulin- β 3 (SEQ ID NO: 7) variants, heregulin γ (SEQ ID NO: 11) variants, heregulin- α (SEQ ID NO: 1) fragments, heregulin- β 1 (SEQ ID NO: 3) fragments, heregulin- β 2 (SEQ ID NO: 5) fragments, heregulin- β 2-like polypeptide (SEQ ID NO: 9) fragments, heregulin- β 3 (SEQ ID NO: 7) fragments, heregulin γ (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments.

15. (Amended) The method of claim 14, wherein the activating ligand is a heregulin- α variant, heregulin agonist antibody or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- α variant is selected from the group of heregulin- α variants having an amino acid substitution, deletion or insertion at one or more amino acid residues corresponding to positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, 43, 45, 46, 48, 49, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226-254, 256-265, 272, 273, 278, 279, 285-309, 437, and 608-611 in the heregulin- α amino acid sequence of SEQ ID NO: 1.

16. (Amended) A method of treating a hair cell related hearing disorder, comprising administering to a patient in need thereof an effective amount of an isolated HER2 and/or HER3 activating ligand comprising a heregulin polypeptide selected from the group consisting of heregulin- β 2 (SEQ ID NO: 5), heregulin- β 2-like polypeptide (SEQ ID NO: 9), heregulin- β 3 (SEQ ID NO: 7), heregulin γ (SEQ ID NO: 11), heregulin- α (SEQ ID NO: 1) variants, heregulin- β 1 (SEQ ID NO: 3) variants, heregulin- β 2 (SEQ ID NO: 5) variants, heregulin- β 2-like polypeptide (SEQ ID NO: 9) variants, heregulin- β 3 (SEQ ID NO: 7) variants, heregulin γ (SEQ ID NO: 11) variants, heregulin- α (SEQ ID NO: 1) fragments, heregulin- β 1 (SEQ ID NO: 3) fragments, heregulin- β 2 (SEQ ID NO: 5) fragments, heregulin- β 2-like

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polypeptide (SEQ ID NO: 9) fragments, heregulin- β 3 (SEQ ID NO: 7) fragments, heregulin γ (SEQ ID NO: 11) fragments, heregulin agonist antibody and heregulin agonist antibody fragments.

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17. (Amended) The method of claim 16, wherein the activating ligand is a heregulin- α variant, heregulin agonist antibody or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- α variant is selected from the group of heregulin- α variants having an amino acid substitution, deletion or insertion at one or more amino acid residues corresponding to positions 2, 3, 8, 9, 23, 24, 33, 34, 36, 37, 42, 43, 45, 46, 48, 49, 62-67, 86, 87, 110, 111, 123, 124, 134, 135, 142, 143, 151, 152, 164-166, 170-172, 208-218, 226-254, 256-265, 272, 273, 278, 279, 285-309, 437, and 608- 611 in the heregulin- α amino acid sequence of SEQ ID NO: 1.

Please add the following new claims:

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19. (New) The method of claim 1, wherein the activating ligand is a heregulin- β variant, heregulin agonist antibody, or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- β variant is selected from the group consisting of heregulin- β variants having an amino acid substitution at one or more amino acid residues corresponding to positions S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206, R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, M226, S228, and F229 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3.

20. (New) The method of claim 14, wherein the activating ligand is a heregulin- β variant, heregulin agonist antibody, or fragment thereof capable of binding to the HER2 or HER3 receptor, wherein said heregulin- β variant is selected from the group consisting of heregulin- β variants having an amino acid substitution at one or more amino acid residues corresponding to positions S177, H178, L179, V180, K181, E184, E186, K187, T188, V191, N192, G193, G194, E195, M198, V199, K200, D201, N204, P205, S206, R207, Y208, L209, K211, P213, N214, E215, T217, G218, D219, Q222, N223, Y224, M226, S228, and F229 of SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, or of the mature polypeptide within SEQ ID NO: 3.